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Human Health Hazard Assessment of FT Jet Fuel and Sensory Irritation Study in Mice

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The experiments reported were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

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14. ABSTRACT
FT jet fuel is a synthetic organic mixture produced using the Fischer-Tropsch (FT) process that is being developed to replace or augment petroleum-derived JP-8 jet fuel for military use by the U.S. armed forces. The FT toxicity testing program results are reviewed. The final study, sensory irritation potential in male Swiss-Webster mice, is evaluated. Groups of four mice were exposed for 30 minutes to FT jet fuel vapor/aerosol atmospheres. Group mean exposure concentrations were 2225, 6844 and 9425 mg/m^3. FT jet fuel evoked breathing patterns characteristic of upper airway sensory irritation. The RD_{50} (50 percent respiratory rate depression) value was calculated to be 10939 mg/m^3. JP-8 has an RD_{50} of 2,876 mg/m^3. FT jet fuel is less irritating than JP-8. A health hazard assessment was conducted for FT jet fuel utilizing all of the following studies: dermal irritation test (FT vs. JP-8 vs. 50/50 blend), *in vitro* genotoxicity tests, acute inhalation study, short-term inhalation rangefinder study, *in vivo* genotoxicity test in tandem with the short-term study, 90-day inhalation toxicity study and sensory irritation assay. The sensory irritation RD_{50} was found to be the most sensitive endpoint. Based on the proposed use of FT jet fuel as a 50/50 blend with JP-8, an occupational exposure limit (OEL) for FT jet fuel is recommended at 200 mg/m^3, in concurrence with the current JP-8 OEL of 200 mg/m^3.

15. SUBJECT TERMS
FT, S-8, Fischer-Tropsch, SPK, jet fuel, sensory irritation, RD_{50}, mice, health hazard assessment, risk assessment

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

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PREFACE

Funding for this project was provided through the Air Force Research Laboratory, Propulsion Directorate, Fuels Branch (Dr. Tim Edwards, AFRL/RZPF) and the Alternative Fuels Certification Office (AFMC 77 AESW/LF, now ASC/WNN). This research was conducted under contract FA8601-07-P-0473. The program manager for the contracts was LT Dean Wagner, PhD, U.S. Navy, while he was stationed at the Naval Health Research Center/Environmental Health Effects Laboratory (NHRC/EHEL) Wright-Patterson Air Force Base (AFB) OH. The technical manager for the program under which this project was conducted, Fischer Tropsch (FT) Jet Fuel Toxicity Assessment, was David Mattie, PhD. John Hinz served on the review panel for this program and this project. The authors acknowledge the following individuals who also served on the review panel:

- Gunda Reddy, PhD (USACHPPM, Aberdeen Proving Ground MD);
- David Steup, PhD (Shell Oil Company, Houston TX; Chairman, American Petroleum Institute-Toxicology Task Force); and
- Errol Zeiger, Ph.D., J.D. (Errol Zeiger Consulting, Chapel Hill NC).

The study was conducted in compliance with the United States Environmental Protection Agency (U.S. EPA) Good Laboratory Practices (GLP) Standards (40 CFR Part 792), with few noted exceptions.

The study protocol was designed to be in compliance with the American Society for Testing and Materials (ASTM) Designation E981-04, Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals (ASTM, 2004).

The animal study was approved by the Air Force Surgeon General's Human and Animal Research Panel (protocol number FWR-2009-0001A) and the Hamner Institutes for Health Sciences Institution Animal Care and Use Committee (IACUC) (protocol number 08025). These studies were conducted in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC), in accordance with the Guide for the Care and Use of Laboratory Animals (NRC, 1996a).

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1.0 SUMMARY

FT jet fuel is a synthetic organic mixture produced using the Fischer-Tropsch (FT) process that converts carbon monoxide and hydrogen to liquid hydrocarbons. Also known as FT, synthetic paraffinic kerosene (SPK) or simply S-8, FT jet fuel is being developed to replace or augment petroleum-derived JP-8 jet fuel for military use by the U.S. armed forces.

To ensure that the toxicity program addressed all issues associated with testing a complex mixture such as jet fuel, an expert review panel of toxicologists was established to discuss the toxicity testing program and provide advice on testing procedures. The review panel determined the minimum number of tests required to assess the toxicity of FT jet fuel. The suite of tests included: dermal irritation test (FT vs. JP-8 vs. 50/50 blend), *in vitro* and *in vivo* genotoxicity tests, acute inhalation study, short-term inhalation rangefinder study, 90-day inhalation toxicity study and sensory irritation assay. The results of the first six studies in the suite are reviewed in this document and reported fully elsewhere.

The last requirement of the FT jet fuel toxicity testing program was to characterize, using past data comparison, the potential of FT jet fuel to cause respiratory tract sensory irritation, an assessment based on the American Society for Testing and Materials (ASTM) E981-04, Standard Test Method for Estimating Sensory Irritancy of Airborne Chemicals (ASTM, 2004). Four groups of four male Swiss-Webster mice were each exposed to one of a graded series of concentrations of FT jet fuel in air, presented as an aerosol/vapor mixture. Animals were placed into nose-only plethysmographs for respiratory monitoring during exposures. Exposure duration was 10 minutes to clean, high efficiency particulate air (HEPA)-filtered air, then 30 minutes to FT jet fuel, followed by 10 minutes to HEPA-filtered air. Respiratory rates were measured for 10 minutes prior to exposure to capture normal breathing patterns, as each mouse served as its own control, and for 10 minutes after exposure to observe recovery. The dose/response was calculated by determining the concentration producing a 50 percent decrease (RD_{50}) slower rate of respiratory rate from normal, or the respiratory rate depression for this exposure paradigm.

The vapor/aerosol concentration of FT jet fuel in each exposure was monitored using infrared spectrophotometry. Group mean exposure concentrations were 2225, 6844 and 9425 mg/m^3. FT jet fuel evoked breathing patterns characteristic of upper airway sensory irritation. The RD_{50} value was calculated to be 10,939 mg/m^3. JP-8 has an RD_{50} of 2,876 mg/m^3. The higher value means that FT jet fuel is considerably less irritating in a vapor concentration exposure than JP-8.

A health hazard assessment was conducted for FT jet fuel utilizing all of the following studies: dermal irritation test (FT vs. JP-8 vs. 50/50 blend), *in vitro* genotoxicity tests, acute inhalation study, short-term inhalation rangefinder study, *in vivo* genotoxicity test in tandem with the short-term study, 90-day inhalation toxicity study and sensory irritation assay. The sensory irritation RD_{50} was found to be the most sensitive endpoint. Based on the RD_{50} and the proposed use of FT jet fuel as a 50/50 blend with JP-8, an occupational exposure limit (OEL) for FT jet fuel is recommended at 200 mg/m^3, in concurrence with the current JP-8 OEL of 200 mg/m^3.

2.0 INTRODUCTION

2.1 Jet Fuel Background: The Past as Prologue

A wide variety of petroleum-derived fuels are used by industry and the Department of Defense (DoD). The important kerosene-based fuels are JP-8, JP-5, Jet A and Jet A-1. Currently, JP-8 is the DoD "universal fuel" and is used in airplanes, tanks, stoves, heaters, etc. JP-8 is one of a number of high production volume (HPV) chemicals monitored by the U.S. Environmental Protection Agency (U.S. EPA). The annual consumption by the U.S. DoD and the general economy amounts to 3 to 4 billion gallons/year and approximately 27 to 36 billion gallons/year, respectively, based on 2003 consumption (Corporan, 2006). For reasons of logistics, strategic security, and energy independence, the Air Force wants to augment its supplies of JP-8 with synthetic jet fuels.

One such alternative jet fuel is a synthetic organic mixture produced using the Fischer-Tropsch (FT) process that converts carbon monoxide and hydrogen to liquid hydrocarbons. Also known as S-8 or synthetic paraffinic kerosene (SPK), FT jet fuel is synthesized, producing a more controlled product than for petroleum-derived fuels whose properties and composition can vary because of source (i.e., Alaska versus the Gulf of Mexico versus the Middle East origin). JP-8 fuel contains a mixture of aliphatic and aromatic hydrocarbons. The FT process creates a mixture of aliphatic compounds similar to those found in JP-8, but does not form aromatic compounds (such as benzene or naphthalene compounds) (Hemighaus, 2007). This difference of composition between FT and JP-8 fuel points to a potential difference in the toxicity of the two fuels.

During refueling operations, personnel may be exposed via the dermal and inhalation routes to vapors and aerosols of jet fuel. A number of prior reports of the toxicity and risk assessment for JP-8 exist from research conducted at Wright-Patterson AFB, first at the Aerospace Medical Research Laboratory, Toxic Hazards Division and its onsite contractor in the Toxic Hazards Research Unit (THRU) and later at the Air Force Research Laboratory (AFRL), Human Effectiveness Directorate, Operational Toxicology Branch. There is also information available from industry and academia. Toxicological Profiles with minimum reference levels (MRLs) were developed by the Agency for Toxic Substances and Disease Registry (ATSDR) for JP-4 and JP-7 (ATSDR, 1995) and for JP-5 and JP-8 (ATSDR, 1998). The U.S. Air Force Institute for Operational Health (AFIOH) (Brooks City Base, TX) sponsored two Jet Fuel Conferences, Jet Fuel I in 1999 that defined issues, discussed research and data gaps; and Jet Fuel II in 2001 that presented the results of the Risk Assessment of Acute Exposure to Jet Fuel study and discussed risk management issues.

Two National Research Council (NRC) National Academies of Science Committee on Toxicology (COT) reviews were conducted. The 1996 review was initiated by the U.S. Navy for JP-5, JP-8 and diesel fuel marine (DFM). The COT recommended 350 mg/m^3 as an occupational exposure limit and 1000 mg/m^3 as the short term exposure limit (STEL) (NRC, 1996b). The 2003 review, focused specifically on JP-8, was initiated by the Air Force. The review concluded that exposure to JP-8 near the permissible exposure limit (PEL) was potentially toxic to the

immune, respiratory and nervous systems (NRC, 2003). Based on the COT's recommendation, the Air Force lowered its standard from the 350 mg/m^3 PEL and adopted 200 mg/m^3 as their occupational exposure limit for vapor and a 5 mg/m^3 occupational exposure limit (OEL) for aerosol. While the COT did not address a STEL (NRC, 2003), the Committee did not revoke its previous recommendation (NRC, 1996) for 1000 mg/m^3. The American Conference of Industrial Hygienists (ACGIH) threshold limit value (TLV) (2003) and Air Force Occupational Safety and Health (AFOSH) 48-8 (1997, rescinded 2008), both referenced the COT reviews and incorporated the aerosol/vapor issue, as well as the Alarie (1966, 1973, 1981) upper respiratory tract (URT) sensory irritation endpoint or 50 percent respiratory depression (RD_{50}). The recent review by National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL) captured all previous work (NAC/AEGL, 2011) including RD_{50} data generated by AFIOH for JP-4, JP-8, JP-8+100 and JP-5 (Whitman and Hinz, 2001, 2004). AFIOH also conducted single dose limit tests for JP-7, JP-10 and DFM (Whitman and Hinz, 2004).

2.2 The Challenge of Testing Jet Fuels

There are a number of issues associated with jet fuel toxicity and exposure questions. JP-8 is a complex mixture with many components. The volatility of JP-8 varies across components. The fuel's toxicity could be an attribute of one or of several of its components; or, its toxicity could reflect a property distributed across the whole mixture. Similarly, the risks associated with exposure to jet fuel could be a function of its component fractions or the fuel as a whole. Furthermore, the fuels' components differ in their physico-chemical properties. While oral and dermal studies provide exposure to the whole fuel by direct application, inhalation toxicity studies appear to have left behind constituents that did not easily vaporize. Therefore, it is important to develop testing procedures and techniques for the whole fuel. The FT studies described here atomized the fuel, achieving a mixed vapor and aerosol atmosphere, in order to assure that all of the fuel's components were reflected in the test atmosphere. However, inhalation atmospheres are dynamic and aerosol content can vary with increasing total fuel concentration. It is important to quantify the vapor and aerosol concentrations and incorporate this type of analysis into current inhalation toxicology studies.

2.3 Toxicity Assessment of FT Jet Fuel

To ensure that the toxicological assessment of FT jet fuel addressed all issues associated with testing a complex mixture, an expert panel of toxicologists was established to review and design the toxicity testing program. The expert panel was chaired by David Mattie, PhD, AFRL/711 HPW/RHPB, Wright-Patterson AFB OH. Membership included individuals listed below; the asterisk (*) denotes the existence of a CRADA (Cooperative Research and Development Agreement) between AFRL and the American Petroleum Institute (API).

- John Hinz, U.S. Air Force School of Aerospace Medicine (USAFSAM)/OEHTH, Brooks City Base TX (now USAFSAM/OEHR, Wright-Patterson AFB OH)
- Gunda Reddy, PhD, U.S. Army Public Health Command, Aberdeen Proving Ground MD

- LT Dean Wagner, PhD, MSC, U.S. Navy, NHRC/EHEL, Wright-Patterson AFB OH
- Katherine Kurtz, Navy and Marine Corps Public Health Center, Portsmouth VA
- David Steup, PhD, Shell Oil & Chairman, API-Toxicology Task Force, Houston TX*
- Wayne Daughtrey, PhD, Exxon-Mobil, Annandale NJ*
- Errol Zeiger, PhD, Errol Zeiger Consulting, Chapel Hill NC

2.3.1 Data Set – Traditional Jet Fuels. The expert panel reviewed the toxicological data for JP-8 to determine the data needs for FT jet fuel. Table 1 shows the known data for JP-8 and its related fuels. The data for JP-8 can be found in military handbook MIL-HDBK-510-1A (DoD, 2010). Except for the lack of a chronic and cancer study, the database is complete. Given the fact that JP-8 is not genotoxic, a cancer study is probably not a critical data gap. Based on toxicity data for all jet fuels and the National Toxicology Program dermal two year study of JP-5 (NTP, 1986), military and industry toxicologists do not believe that JP-8 possesses sufficient toxicity to warrant a chronic/life-time study in rodents at this time. According to the COT, data gaps still exist for chronic and carcinogenic studies of JP-8 (NRC, 2003). As such, these endpoints are labeled as potential data gaps.

Table 1. Existence of Toxicological Data for Petroleum Derived Jet Fuels

	JP-5 & 8 Jet A & A-1	**Data Gaps**
Acute	✓	
URT Irritation	✓	
Two-week	✓*	
Subchronic	✓	
Chronic	-	?
Cancer	-	?
Immunological	✓	
Neurological	✓	
Developmental	✓	
Reproductive	✓	
Genotoxic	✓	

Notes: "-" = no data; ✓ = data available; * = technical report by Naval Medical Research Unit (NAMRU)/Dayton is in preparation; ? = potential data gap

2.3.2 Design of FT Studies. The goal of the FT jet fuel toxicology program was to fill enough data categories for FT jet fuel to be able to conduct a comparative health hazard assessment (HHA) between JP-8 and FT jet fuels, and to derive an OEL for the safe use of FT jet fuel. The toxicity program sponsor was the Alternative Fuels Certification Office (AFCO; AFMC ASC/WNN), Wright-Patterson AFB OH.

To develop the appropriate study design for each toxicity test, all testing followed U.S. EPA and the European Organisation for Economic Co-operation and Development (OECD) test guidelines. All studies were conducted according to the U.S. EPA Good Laboratory Practices (GLP). To maximize the effects, all tests used 100 percent FT jet fuel. The studies conducted are listed below and are reviewed in Section 3.0 and 4.0.

- Dermal irritation test (FT *vs*. JP-8 *vs*. 50/50 blend)
- *In vitro* genotoxicity tests
- Acute inhalation study
- Sub-acute inhalation rangefinder study
- *In vivo* genotoxicity test in tandem with sub-acute
- 90-day inhalation toxicity study
- Sensory Irritation Assay

2.4 Sensory Irritation Assay

This report details the results of the Sensory Irritation Assay, the last of the panel's recommended studies for FT jet fuel toxicity. Using an internationally-recognized standard test method (ASTM E981-04, 2004), the sensory irritation potential has been evaluated previously for JP-4, JP-8, and JP-8+100 (Whitman and Hinz, 2001). The concentration that produces a 50 percent decrease in respiratory rate or RD_{50} varies with the type of jet fuel. For example, the RD_{50} value for JP-8 was 2876 mg/m^3, but for JP-4 the RD_{50} value was 4842 mg/m^3, an approximate two-fold difference in potency. Since inhalation will be a major route of exposure for FT jet fuel, the assessment of sensory irritation of FT by inhalation is needed to evaluate the risk of replacing or augmenting JP-8 by FT fuel. This study is designed to assess the sensory irritation potential of FT when administered via inhalation exposure to mice once for periods up to 30 minutes duration.

3.0 FT JET FUEL TOXICITY TESTS

3.1 Dermal Irritation/Toxicity

The dermal study was the one study in which 100 percent FT jet fuel, 100 percent JP-8 and a 50/50 mixture of FT/JP-8 were all tested due to past issues with JP-8 dermal irritation and because of the inexpensive cost of this assay, as compared to other toxicity studies. The review panel recommended conducting the study using both occluded and semi-occluded exposures. In the dermal irritation test, each animal serves as its own control as test patches are randomly assigned to a different fuel/mixture or control (no fuel). The Primary Irritation Index was calculated to assign a descriptive rating to each test article and the mixture. Based on the Irritation Index, FT jet fuel and the 50:50 blend are either the same as JP-8 or less irritating (Table 2). The final report for dermal irritation is found in Hurley *et al.* (2011).

Table 2. Dermal Irritation Comparison Chart for JP-8, FT Jet Fuel and 50/50 Blend

	JP-8	FT	JP-8/FT
Occluded			
Irritation Index	2.1	2.3	1.9
Descriptive Rating	moderate	moderate	slight
Semi-Occluded			
Irritation Index	1.8	0.8	1.5
Descriptive Rating	slight	slight	slight

3.2 *In Vitro* Genotoxicity

Two studies were conducted *in vitro* to test for genotoxicity. The Ames Test (reverse mutation assay) is designed to establish the potential to induce point gene mutations in a standard bacterial test using four strains of *Salmonella typhimurium* and one strain of *Escherichia coli*. The results demonstrated no toxic or mutation effects in any of five test strains (Mattie *et al.*, 2011a). Another study tested five different alternative bio-based fuels for mutagenicity; S-8 (FT) jet fuel was one of the five. This study also found no evidence of mutagenicity in FT jet fuel or the other four fuels (Riccio *et al.*, 2010).

The chromosomal aberration test examined the potential to induce chromosomal aberrations in human lymphocytes. The results showed that no chromosomal aberrations were induced by FT jet fuel, so it is not clastogenic (Mattie *et al.*, 2011a).

3.3 Inhalation Toxicity

The inhalation studies exposed animals to all of the constituents of the FT jet fuel by aerosolizing the fuel into an aerosol/vapor mixture. The chambers were characterized for vapor and aerosol concentrations, partitioning, fingerprints and particle size. The results of the fingerprint analyses for the short term (acute and two-week) and 90-day (subchronic) studies are found in reports by Mattie *et al.* (2011b and 2012, respectively). Aerosol and vapor phase FT jet fuel samples were collected from high the 2000 mg/m^3, 1000 or 700 mg/m^3 and the 500 or 200 mg/m^3 concentration groups for the purpose of qualitatively comparing the various samples using GC/MS analysis. A number of observations were made based on the analysis of the collected samples. The aerosol phase reflected the presence of higher molecular weight, less volatile compounds compared to the vapor phase. This trend was observed at all three exposure concentrations across the inhalation studies. There did not appear to be an appreciable difference in the distribution of compounds when comparing the different aerosol fractions from each concentration group. In the vapor phase, there appeared to be more total compounds present in the high concentration exposure samples compared to the low concentration exposure samples, perhaps reflecting their emergence above the threshold of detection. A majority of the compounds (accounting for >90% of the total peak area in the sample) found in the low concentration vapor samples were those found between n-undecane and n-tetradecane, while the

high concentration vapor samples appeared to contain a much larger range of molecular weight compounds (n-octane through n-pentadecane).

3.3.1 Acute Inhalation Study. The acute inhalation study was a 4 hour exposure of 5 male and 5 female rats to the limit test dose of 2000 mg/m^3. No clinical symptoms were observed, so this dose became the high dose in the two-week rangefinder study (Mattie *et al.*, 2011b).

3.3.2 Two-week Study. Building on the results from the acute study, the two-week study targeted exposure concentrations at 2000, 1000, and 500 mg/m^3 for high, mid and low exposure groups, respectively. In turn, the two-week study served as a rangefinder for the 90-day study, while also providing the method of exposure for the micronuclei assay, a genotoxicity test that is conducted *in vivo*. A complete report of this study may be found in Mattie *et al.* (2011b). Table 3 summarizes the actual average exposure concentrations achieved for the inhalation exposure as well as the additional animals needed for the micronuclei study.

Table 3. Study Design for the Two-Week FT Jet Fuel Inhalation Study with Micronucleus Experiment

Group	**Exposure Level**	**Number of Animals**	
	(mg/m^3, mean ± SD)	**Males**	**Females**
Control	0	5	5
Low	497.0 ± 8.4	5	5
Intermediate	999.0 ± 19.9	5	5
High	1958.1 ± 41.8	5	5
Micronuclei Negative Control	0	5	5
Micronuclei Positive Control	0	5	5
Total		30	30

Note: SD = standard deviation

For the two-week study, endpoints were observations before and after exposures for overt signs of toxicity. Tissues and organs were examined for gross pathology: nasal airways, trachea, larynx, lungs, liver, kidney, spleen, adrenals and heart. Few gross findings considered unrelated to treatment were noted.

Bone marrow from the femur was examined as part of the micronuclei induction assay. Positive control animals responded with micronuclei induction. No micronuclei were seen as a result of

two weeks of inhalation exposure to FT jet fuel, or from negative control animals. This confirms the *in vitro* data that FT jet fuel is non-genotoxic.

Body weight changes were only seen in the high dose rats. There was no change in food consumption. All animals survived to the end of the study.

FT jet fuel had no adverse effects on the trachea, larynx, spleen, adrenals and heart. The liver in all exposed males showed hepatocyte hypertrophy. This liver effect was only seen in the highest dose female rats. In the kidney, hyaline droplets were seen in the proximal convoluted tubules of all exposed males. This was expected as it is a male rat specific effect seen after exposure to hydrocarbon fuels. Hyaline droplets were not seen in female rats and are not expected to be seen in humans, male or female, as humans do not have the protein that produces the hyaline droplets (Baetcke *et al.*, 1991).

The incidence of inflammatory cell infiltration in the lungs is shown in Table 4. The effect starts out as a focal or single infiltrate and progresses to multiple sites or multifocal inflammatory cell infiltration. There was no effect in the low dose for either male or female rats. The intermediate dose had little effect in both males and females, while the high dose group had 100 percent incidence of multifocal infiltration in both sexes. However, the severity in the multifocal inflammatory cell infiltration was only minimal to mild (1 to 2 on a scale of 1 to 5, with 5 being severe).

Table 4. Incidence of Lung Inflammatory Cell Infiltration in FT Jet Fuel Two-Week Inhalation Study

Group [mg/m^3]	Multifocal Inflammatory Cell Infiltration	Focal Inflammatory Cell Infiltration
Males		
Control [0]	0	0
Low [500]	0	0
Intermediate [1000]	1	1
High [2000]	**5**	**0**
Females		
Control [0]	0	0
Low [500]	0	0
Intermediate [1000]	0	2
High [2000]	**5**	**0**

Note: n = 5/group/sex

For the nasal cavity, the incidence of olfactory degeneration can be seen in Table 5. The severity of this effect was minimal (1 out of 5) at 1000 mg/m^3 and mild (2 out of 5) at 2000 mg/m^3. The

levels correspond to Figure 1; only levels II through IV contain olfactory epithelium. The lowest dose showed no effects while the intermediate dose had variable incidence. The highest dose group incidence was 4 to 5 of 5 (80 to 100 percent incidence). Since the severity of olfactory degeneration was still only mild (2 out of 5 with 5 being severe) in the highest dose group, this concentration of 2000 mg/m^3 was chosen for the highest dose group in the 90-day study.

Table 5. Incidence of Olfactory Degeneration in FT Jet Fuel Two-Week Inhalation Study

Group [mg/m^3]	Level II	Level III	Level IV
Males			
Control [0]	0	0	0
Low [500]	0	0	0
Intermediate [1000]	2	2	0
High [2000]	**4**	**5**	**5**
Females			
Control [0]	0	0	0
Low [500]	0	0	0
Intermediate [1000]	2	4	4
High [2000]	**5**	**5**	**4**

Note: n = 5/group/sex

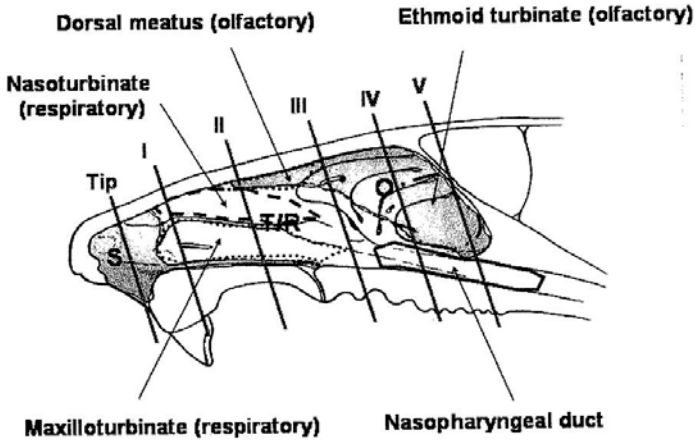

Figure 1. Levels of the Rat Nasal Cavity
Adapted from Morgan (1991).

3.3.3 90-Day Inhalation Toxicity. The 90-day study is the first of two primary studies conducted for the FT jet fuel HHA and OEL determination. The 90-day study design was based on U.S. EPA and OECD test guidelines. It included a full histopathology list, per guidelines, but also conducted were a neurotoxicity screening battery with motor activity and the functional observation battery, as well as sperm morphology and vaginal cytology to address data gaps for reproductive endpoints. A complete report of this study can be found in Mattie *et al.* (2012).

FT jet fuel was administered as an aerosol/vapor combination for 6 hours per day for 5 days per week for 13 weeks. Male and female rats were exposed to three concentrations targeted at high (2000 mg/m^3), intermediate (700 mg/m^3) and low (200 mg/m^3), with a control group (0 mg/m^3). Table 6 shows the target and actual exposures for each group. The rats were placed in two subgroups for each dose to allow a staggered start and finish to permit sufficient time at the end of the exposures to collect all of the samples.

Table 6. Study Design for the 90-Day FT Jet Fuel Inhalation Study

Group*	**Exposure Level (mg/m^3)**		**Number of Animals***	
	Target	**Actual (mean ± SD)**	**Males**	**Females**
Control	0	0.02 ± 0.1	5	5
Control			5	5
Low Dose	200	200 ± 0.1	5	5
Low Dose			5	5
Intermediate Dose	700	698 ± 16.7	5	5
Intermediate Dose			5	5
High Dose	2000	1988 ± 48.1	5	5
High Dose			5	5
TOTAL			40	40

Note: *Groups of 10 were split in half and starting times were staggered to allow sufficient time to collect data at the end of exposure.

All animals were observed before and after exposures for overt signs of toxicity. A body weight decrease was seen only at the 2000 mg/m^3 dose. Tissues and organs examined at necropsy for gross pathology showed no biologically significant changes. Blood collected for clinical pathology had no biologically significant changes.

Male rat kidneys were analyzed for α2μ-globulin, the male rat protein that produces hyaline droplets after hydrocarbon exposure. Although α2μ-globulin was present, it was not seen at the levels expected or those seen with other hydrocarbons such as JP-8. FT jet fuel is considered a weak inducer of hyaline droplets compared to JP-8.

Although a full list of tissues were collected for histopathology, significant changes were only seen in the nasal cavities and lungs, primarily in rats exposed to 2000 mg/m^3. Table 7 shows incidence and severity for olfactory epithelial degeneration and hypertrophy and/or hyperplasia of goblet cells and nasopharyngeal ducts. The trend was the same as for the two-week study. There were no effects at the lowest dose, minimal effects (1 out of 5) at the intermediate dose with variable incidence and mild effects (2 out of 5) at the high dose with 100 percent incidence.

Table 7. Incidence and Severity of Nasal Histopathology in FT Jet Fuel 90-Day Inhalation Study

Group [mg/m^3]	**Olfactory Epithelial Degeneration**		**Hypertrophy/Hyperplasia of Goblet Cells, Nasopharyngeal Duct**	
	Incidence/Severity		**Incidence/Severity**	
	Males	**Females**	**Males**	**Females**
Control [0]	0	0	0	0
Low Dose [200]	0	0	0	0
Intermediate Dose [700]	9/minimal	8/minimal	10/minimal	9/minimal
High Dose [2000]	10/slight-mild	10/slight-mild	10/slight-mild	10/slight-mild

Note: n = 10/group/sex

Table 8 shows incidence for inflammatory cell infiltration in the lungs. The trend is the same as seen at two weeks. The effect starts out as a focal or single infiltrate and progresses to multiple sites or multifocal inflammatory cell infiltration. There was no effect in the low dose for female rats. Only one male rat out of ten in the low dose group had a focal inflammatory cell infiltration. The intermediate dose had little effect in both males (10 percent) and females (30 percent) while the high dose group had 100 percent incidence of multifocal infiltration in both sexes. However, the severity of the focal inflammatory cell infiltration was only minimal (1 on a scale of 1 to 5 with 5 being severe). The severity of the multifocal inflammatory cell infiltration was only minimal to mild (1 to 2 on a scale of 1 to 5, with 5 being severe).

Table 8. Incidence of Lung Histopathology in FT Jet Fuel 90-Day Inhalation Study

Group [mg/m^3]	Multifocal Inflammatory Cell Infiltration		Focal Inflammatory Cell Infiltration	
	Incidence		Incidence	
	Males	Females	Males	Females
Control [0]	0	0	0	0
Low Dose [200]	0	0	1	0
Intermediate Dose [700]	0	0	1	3
High Dose [2000]	10	10	0	0

Note: n = 10/group/sex

Motor activity and the functional observational battery assess neurobehavioral effects. Although a number of endpoints were different than control levels, the only significant changes seen were in the 2000 mg/m^3 rats. This exposure is very high and was given for a long period of time; this animal exposure is not representative of human exposure. Therefore, any changes seen at this high dose are not expected to be a potential hazard to humans. However, neurobehavioral endpoints will be considered in future jet fuel studies to ensure that there is no human health hazard.

Sperm morphology examinations were conducted as an additional endpoint to address potential reproductive effects. Samples were stained and examined for abnormal sperm. No effects were seen in sperm indicating normal sperm production in male rats. Vaginal cytology looks for alterations in the estrous cycle and is assessed by examination of cells from vaginal smears. No effects were seen in the vaginal smears, indicating normal estrous cycles in female rats. While these tests were valuable additions to the 90-day study, they do not address all reproductive endpoints such as fertility and do not address any development effects.

4.0 SENSORY IRRITATION STUDY

The URT sensory irritation assay is the second of two primary studies conducted for the FT jet fuel HHA and OEL determination. This study does not have a U.S. EPA or OECD guideline, but does have an ASTM standard (E-981-04, 2004), which was derived from Alarie (1966, 1973) based on the dose response for breathing rate depression. Alarie (1981) established a correlation of RD_{50} values with existing TLVs and OELs.

4.1 Sensory Irritation Methods

FT jet fuel (CAS No. 437986-20-4) was obtained from Syntroleum Corporation (Tulsa OK). An additive package consisting of chemicals normally added to JP-8 jet fuel was added to the FT jet

fuel by the Fuels Branch at Wright Patterson AFB. The combination of FT jet fuel with additives was designated POSF 5109. The FT jet fuel with additives was shipped in a five gallon drum to the test facility and stored in a well-ventilated area at room temperature. The FT jet fuel used in the toxicity evaluation was determined to be stable before and after the 90-day toxicity study (Mattie *et al.*, 2012); the same lot was used for this study. The jet fuel was not diluted prior to use.

4.1.1 Animals and Animal Husbandry. A total of 29 male Swiss-Webster mice (Crl:CFW(SW)) were obtained from Charles River, Kingston NY. Animal weights ranged from 22.2 to 28.2 g the day after receipt. Animals were acclimated to the facility for approximately two weeks. During the acclimation period, animals were group-housed (2 to 3 per cage) in shoebox (micro-isolation) cages. Mice were acclimated to modified nose-only plethysmographs tubes (Model 3381, Buxco Research Systems, Wilmington NC) for one hour on the day preceding the start of exposures. Mice were approximately 7 to 8 weeks of age with weights ranging from 27.5 to 37.8 g at time of exposure. Since the weight range was still fairly narrow and the slightly larger size of the mice did not impact their positioning in the nose only exposure tubes, this exception to ASTM E981-04 (2004) had no effect on the results of the study.

Room conditions were maintained between 20 and 24 °C, 30-70 percent humidity, with a 12 hour light/dark cycle. Animals were fed a certified rodent diet, NIH-07 (pellets, Zeigler Brothers, Gardners PA), and reverse osmosis purified municipal tap water, *ad libitum*, except during exposure, when food was withheld. Certification of analysis of feed batch was supplied by the manufacturer. There were no known contaminants in the feed that were expected to interfere with the results of this study. Drinking water analyses were conducted quarterly by an independent laboratory. There were no known contaminants in the drinking water that were expected to interfere with the results of this study. Documentation of these analyses is maintained on file at The Hamner Institutes and applicable copies are kept with the study files.

The Hamner Institutes facility is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International (AAALAC), and all procedures involving live animals were in compliance with the Guide for the Care and Use of Laboratory Animals (NRC, 1996a). The study-specific protocol was approved by the Institutional Animal Care and Use Committee (IACUC).

4.1.2 Exposures. Animals were loaded into nose-only plethysmographs, which isolated the animal head from its body via a latex dam. The plethysmographs were placed onto the nose-only exposure tower. Animal breathing signals were captured by a differential pressure transducer, amplified, digitally recorded and analyzed by the BioSystem XA software (Version 2.7.9, Buxco Research Systems, Wilmington NC). Each exposure group was monitored in the following sequence: 10 minutes of room air for a baseline, 30 minutes of exposure to FT jet fuel and 10 minutes of room air to monitor recovery.

Dilution air for exposures was pulled by fans at approximately 200 L/minute through a 95 percent high efficiency particulate air (HEPA) filter and a charcoal filter, the temperature and

humidity adjusted, as required, and distributed to the exposure system. Exposure atmospheres were generated, mixed with the dilution air and delivered into a 1 m^3 steel and glass inhalation chamber. The inhalation chamber was used to further mix exposure atmospheres. Atmospheres were then drawn from the inhalation chamber to the nose-only exposure tower (Jaeger-NYU, CH Technologies Inc, Westwood NJ) at approximately 2 L/minute.

Temperature and relative humidity were measured at the nose-only tower by a Rotronic Humidity Sensor (Series 200, Rotronic Instrument Corp., Huntington NY) connected to the Continuum Building Automation System (Andover Controls Corporation, Andover MA). Temperature and humidity ranges were 67.3 to 68.7°F and 45.7 to 47.7 percent relative humidity, respectively, for all exposures.

4.1.3 Generation System. The FT jet fuel was generated as either a vapor or vapor/aerosol mixed atmosphere in air. Vapor atmosphere was generated (Figure 2) by using a fluid metering intake (FMI) pump (Fluid Metering, Inc, Syosset NY) to deliver the FT from a reservoir bottle to the inside surface of a heated metal tube filled with 6 mm glass beads. The outside of the metal tube was heated with a heating jacket to a constant temperature of 82°C and monitored by thermometer. The jet fuel was volatized and the resulting vapors drawn into the delivery system by house air moving upward through the tube. The vapor was carried by dilution air into an inhalation chamber and then drawn into a nose-only exposure tower.

The mixed vapor/aerosol atmospheres were generated (Figure 3) as a liquid droplet aerosol using an air-atomizing nozzle (Model SUJ1A with fluid cap 1650 and air cap 64, Spraying Systems Co., Wheaton IL). The FMI pump delivered jet fuel from a glass bottle reservoir to the nozzle. Compressed instrument air at approximately 50 psi was supplied to the nozzle. The nozzle assembly was housed in a stainless steel sanitary tee fitting. The spray was directed into a custom-made glass tube of approximately 13 liters, carried by dilution air into an inhalation chamber to facilitate thorough mixing and then drawn into a nose-only exposure tower.

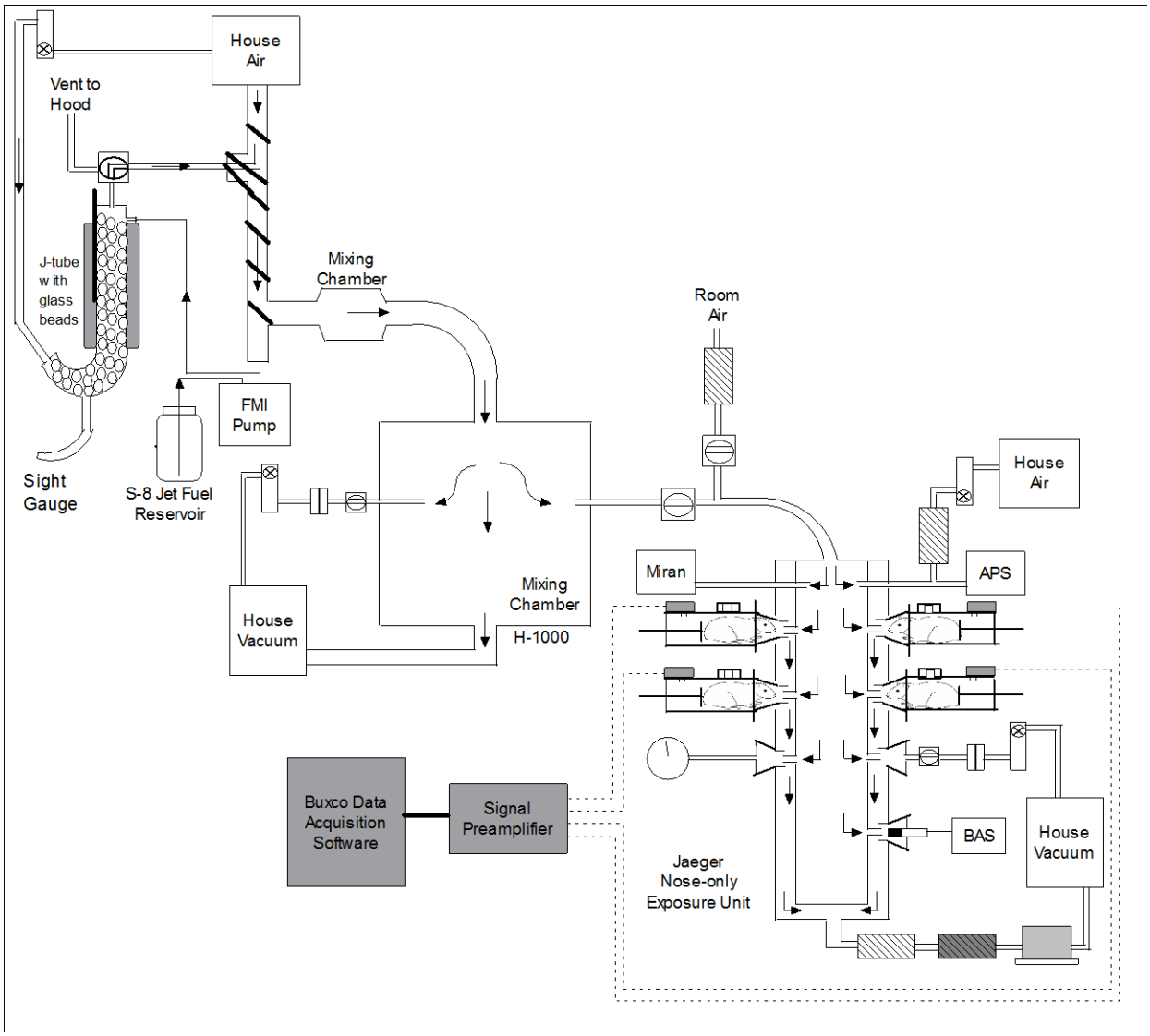

Figure 2. FT Jet Fuel Vapor Generation and Exposure System

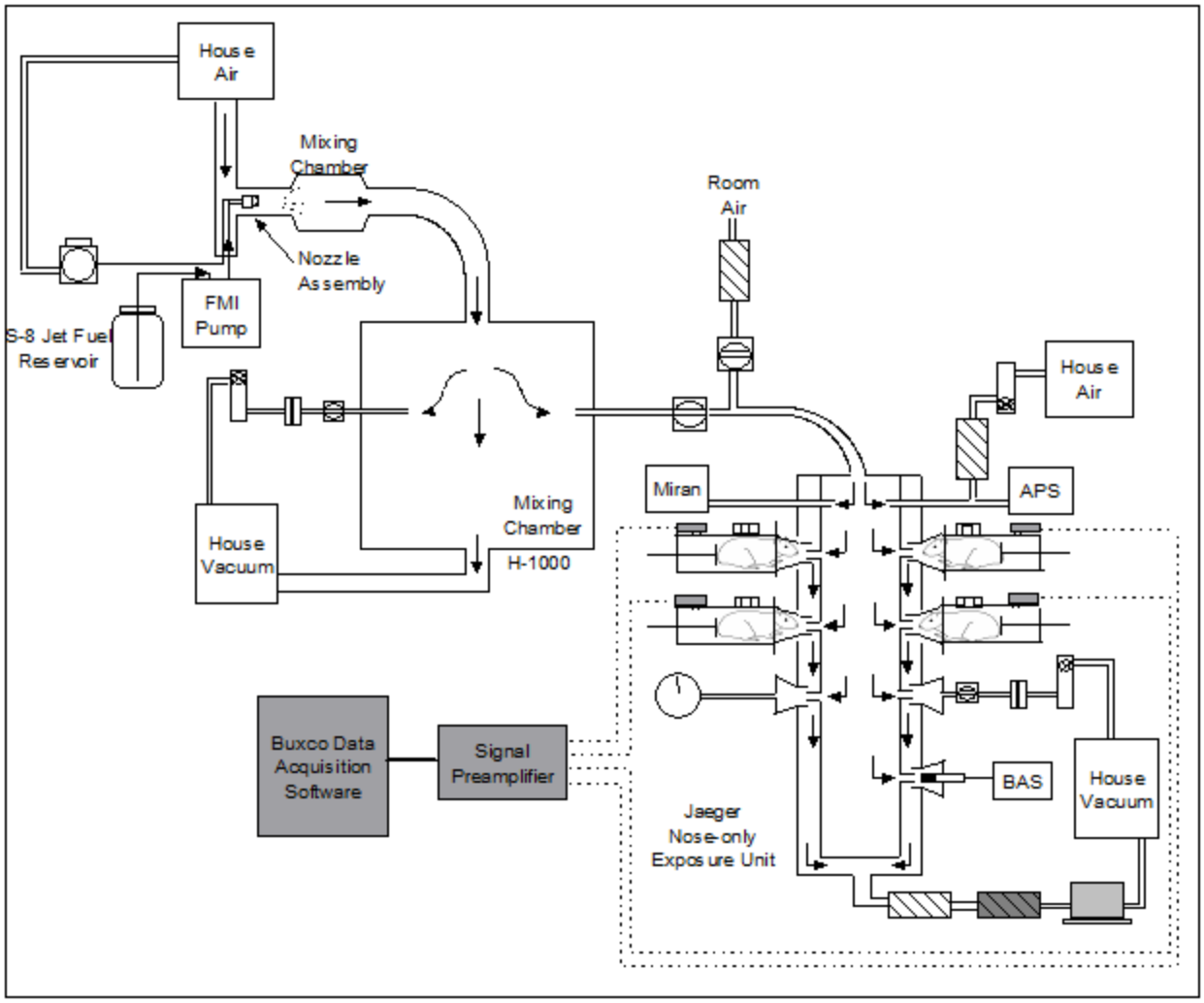

Figure 3. FT Jet Fuel Aerosol/Vapor Generation and Exposure System

4.1.4 Concentration Determination. An infrared spectrophotometer (MIRAN 1A, Foxboro Co., South Norwalk, CT) was used to monitor the total concentration (aerosol and vapor) of jet fuel at the nose-only exposure unit. The sensing cell of the infrared (IR) spectrophotometer was warmed to approximately 50°C by a heat tape. A sample of the chamber atmosphere was pulled through the IR spectrophotometer. When the sample was pulled through the heated cell, the aerosol droplets evaporated. A chart recorder was used to continuously record the electrical output of the IR spectrophotometer. Dilution air was added for the higher concentration atmospheres in order to keep the aerosol concentration within range of the instrument.

Mass weight (gravimetric) filter samples were used to determine the concentration of the non-volatile aerosol. Filters were collected from a port on the nose-only exposure unit for each of the exposures.

Nominal concentration was calculated from the airflow rate through the chamber and the FMI pump rate.

4.1.5 Particle Sizing Analysis. Particle size distribution measurement was conducted using an aerodynamic particle sizer (APS, Model 3321, TSI, Inc., Shoreview MN). The instrument was connected to the inside of the nose-only exposure unit. Dilution air was added in order to keep the aerosol concentration within the operating range of the instrument.

4.1.6 Animal Response Evaluation. During exposures, animals were placed into plethysmograph tubes. As the animal's body expanded and contracted during normal breathing, the pressure in the plethysmograph fluctuated accordingly. Pressure fluctuations forced air to flow through an opening at the top of the plethysmograph. These airflows passed through a stainless steel mesh pneumotachograph. The pressure difference across the pneumotachograph was detected by a pressure transducer, which converted the pressure differential to an electrical signal. The electrical signal was captured by the data acquisition system. The electrical signal was in the form of the animals breathing pattern. The breathing patterns were recorded and analyzed for respiratory rates by the BioSystem XA software (Version 2.7.9, Buxco Research Systems, Wilmington NC). The equipment was also purchased from Buxco.

The baseline respiratory rates were averaged over the last six 15-second intervals immediately preceding the exposure period. Exposure respiratory rates were averaged at 15-second intervals for the first five minutes and at 3-minute intervals for the remainder of the exposure period. Post-exposure breathing rates were averaged at 1-minute intervals for 10 minutes.

The average baseline respiratory rate, the lowest representative respiratory rate during the exposure and the highest post-exposure rate were determined for each animal in a group. The lowest representative breathing rate and the highest post-exposure rates were each divided by the baseline rate to obtain a "percent of baseline" value. The percent of baseline value was subtracted from 100 percent to yield the response by each animal (percent decrease in respiratory rate).

4.1.7 Statistical Analysis. The mean group responses and exposure concentrations were entered into a least squares analysis to determine the concentration of exposure material needed to reduce respiratory rate by 50 percent, the 95 percent confidence limits, the slope function of the plotted data, and the fit of the data from the experiment (Snedecor and Cochran, 1989).

4.2 Sensory Irritation Results

4.2.1 Exposure Concentrations. Five groups of 4 male mice were exposed for 30 minutes to total analytical concentrations of 736 (vapor only), 2225, 4749, 6844 or 9425 mg/m^3 (vapor and aerosol). The proportion of aerosol increased with increasing total concentration, from 0.5

percent at 736 mg/m^3 to 36 percent at 9425 mg/m^3 (Table 9). The mass median aerodynamic diameter ranged from 1.15 to 1.98 µm, which is respirable in size. Note that for one concentration (4749 mg/m^3), only nominal concentration data were available due to a malfunction of the infrared spectrophotometer.

Table 9. Summary of Atmosphere Exposure Data

Mean Concentration (mg/m^3)	**9425.1**	**6843.6**	**4749.3****	**2224.7**	**736.3***
Standard Deviation	296.6	238.7		10.0	12.9
Coefficient of Variation (%)	3.15	3.49		0.45	1.75
Total Concentration (mg/m^3)	9425.1	6843.6	4749.3	2224.7	736.3
Aerosol Concentration (mg/m^3)	3428.5	2405.2	1548.2	395.2	3.4
% Aerosol	36.4	35.1	32.6	17.8	0.5
Percent Respiratory Rate Decrease	-53	-33	-41	-20	-10
Percent Recovery to Baseline	64	74	72	102	110
Mass Median Aerodynamic Diameter (µm)	1.54	1.85	1.98	1.15	0.79***
Geometric Standard Deviation	1.47	1.53	1.55	1.41	1.26***
RD_{50} (mg/m^3)	11661				
95% Confidence Interval	6885 to 38103				

Notes: *Exposure atmosphere generated as vapor only; **Due to difficulties with Miran, concentration was calculated by nominal calculation; ***A small number of particles were detected by APS during the vapor only exposure (0.08 aerosol particles/cm^3)

4.2.2 Animal Response Data. The summary data for the decrease in breathing rate for each animal, at the concentrations tested, are shown in Table 10. Figures 4 through 8 present graphs of the individual respiratory rates. Figure 9 shows the mean respiratory decrease for each group as a percentage of the group's baseline.

Table 10. Summary of Animal Response Data

Concentration (mg/m^3)	Animal Number	Body Weight (g)	% Respiratory Decrease	% Recovery	Irritation Type**	Gross Observations*
9425.1	20	31.6	-40	84.4	Sensory/Moderate	NOA
	21	31.3	-65	57.2	Sensory/Extreme	NOA
	22	30.0	-47	64.1	Sensory/Moderate	NOA
	23	34.1	-60	51.6	Sensory/Extreme	NOA
	Mean	31.8	-52.8	64.3		
	S.D.	1.7	11.3	14.3		
6843.6	12	32.0	-51	61.9	Sensory/Extreme	NOA
	13	29.6	-42	54.7	Sensory/Moderate	NOA
	14	32.3	-36	73.1	Sensory/Moderate	NOA
	15	31.4	-3	106.1	Sensory/None	NOA
	Mean	31.3	-33.0	74.0		
	S.D.	1.2	21.0	22.7		
4749.3	8	33.5	-40	70.8	Sensory/Moderate	NOA
	9	30.9	-33	75.6	Sensory/Moderate	NOA
	10	31.3	-57	55.6	Sensory/Extreme	NOA
	11	31.9	-33	84.5	Sensory/Moderate	NOA
	Mean	31.9	-40.8	71.6		
	S.D.	1.1	11.3	12.1		
2224.7	1	31.1	-6	107.3	Sensory/Slight	NOA
	2	30.5	-34	82.4	Sensory/Moderate	NOA
	6	28.1	-26	113.3	Sensory/Moderate	NOA
	7	32.6	-16	105.9	Sensory/Slight	NOA
	Mean	30.6	-20.5	102.2	Sensory/Moderate	
	S.D.	1.9	12.1	13.6		
736.3	24	30.9	-8	105.5	Sensory/None	NOA
	26	30.2	-14	116.9	Sensory/Slight	NOA
	27	37.8	2	117.3	Sensory/None	NOA
	28	36.3	-20	100.6	Sensory/Moderate	NOA
	Mean	33.8	-9.6	110.1		
	S.D.	3.8	9.4	8.3		

Notes: *NOA – no observable abnormalities seen before, during or after exposures; **severity categorized as slight = 12-19%; moderate = 20-49%; extreme ≥ 50%

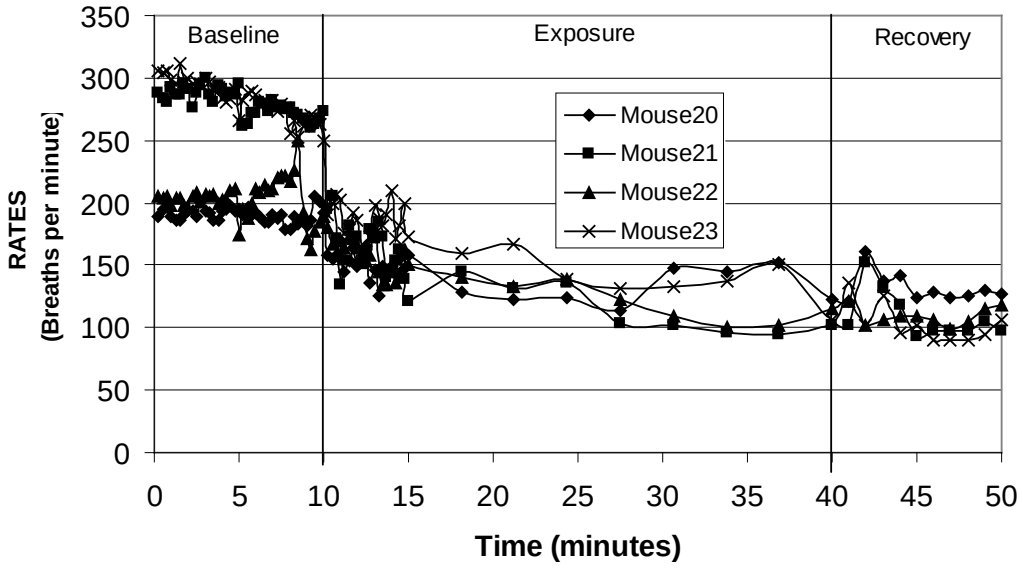

Figure 4. Individual Respiratory Rates for 9425 mg/m^3 exposure

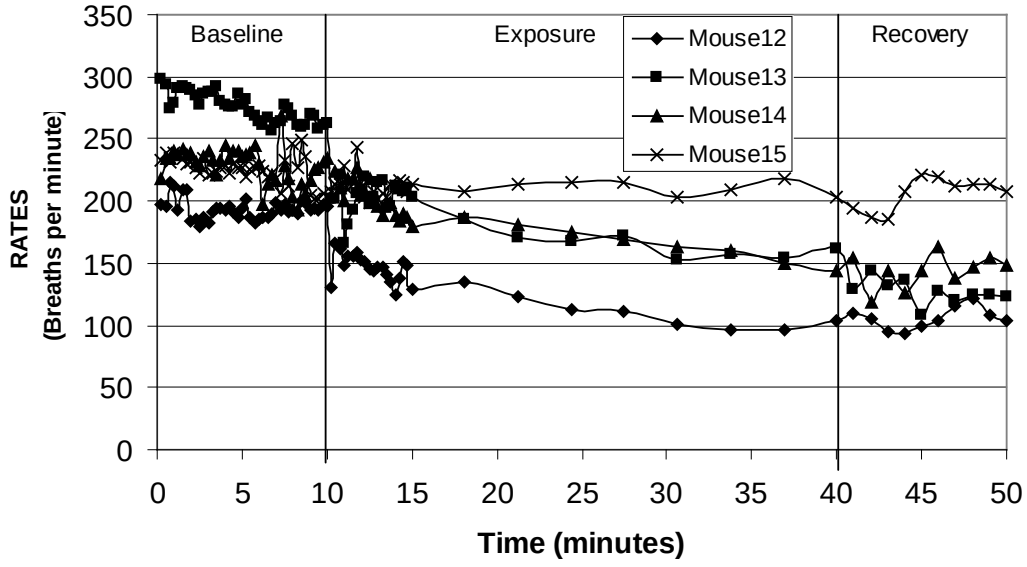

Figure 5. Individual Respiratory Rates for 6844 mg/m^3 exposure

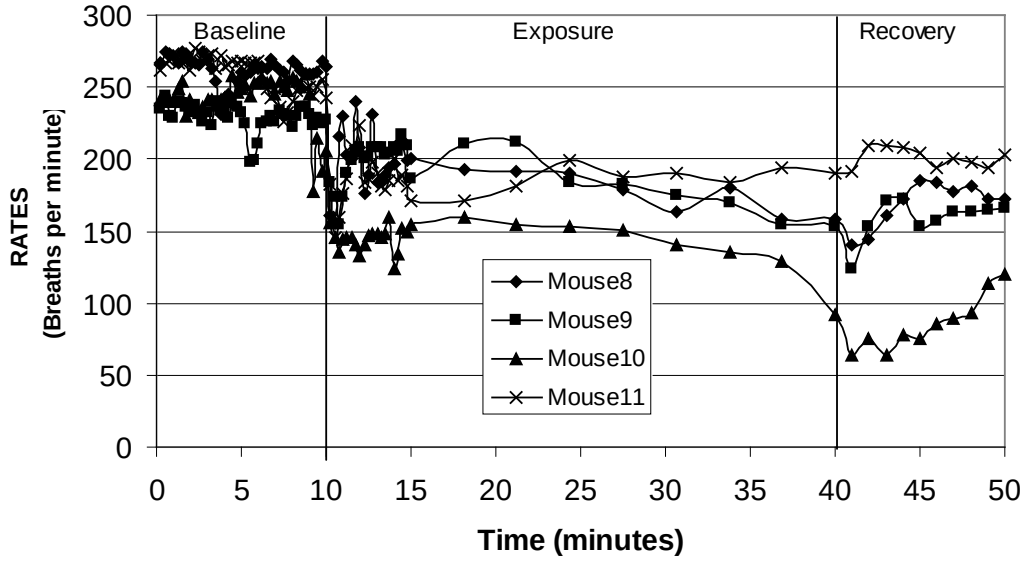

Figure 6. Individual Respiratory Rates for 4749 mg/m^3 exposure

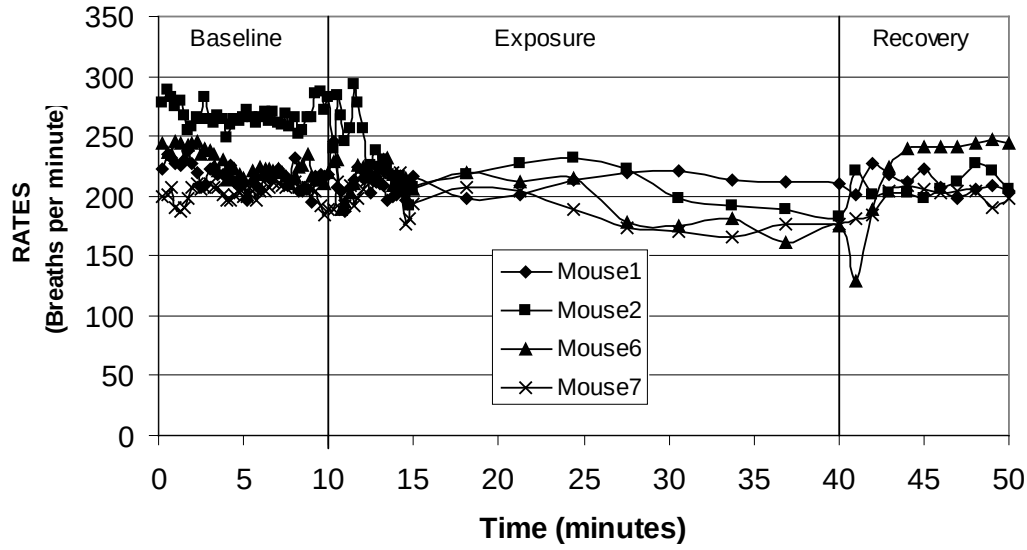

Figure 7. Individual Respiratory Rates for 2225 mg/m^3 exposure

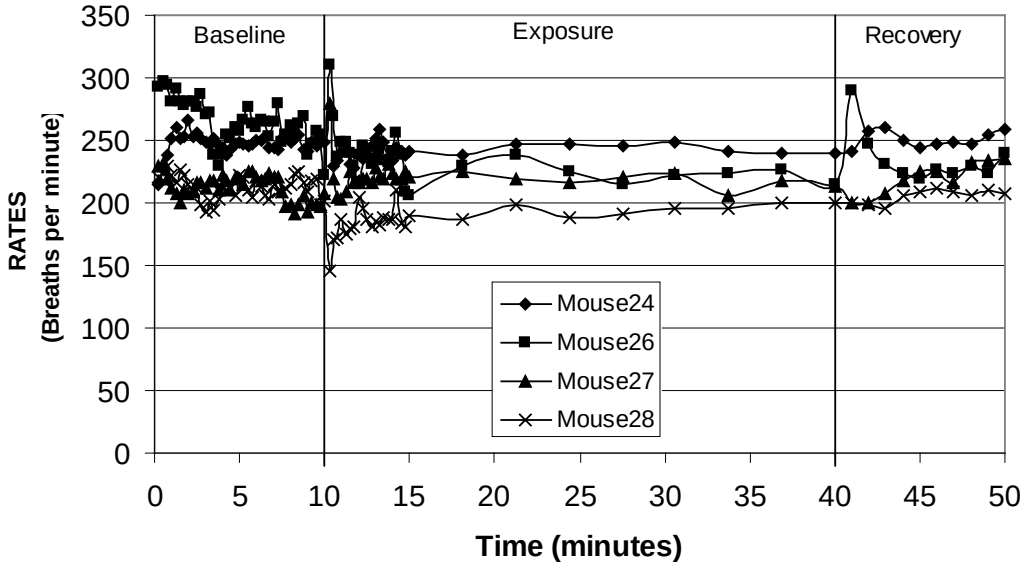

Figure 8. Individual Respiratory Rates for 736 mg/m^3 vapor only exposure

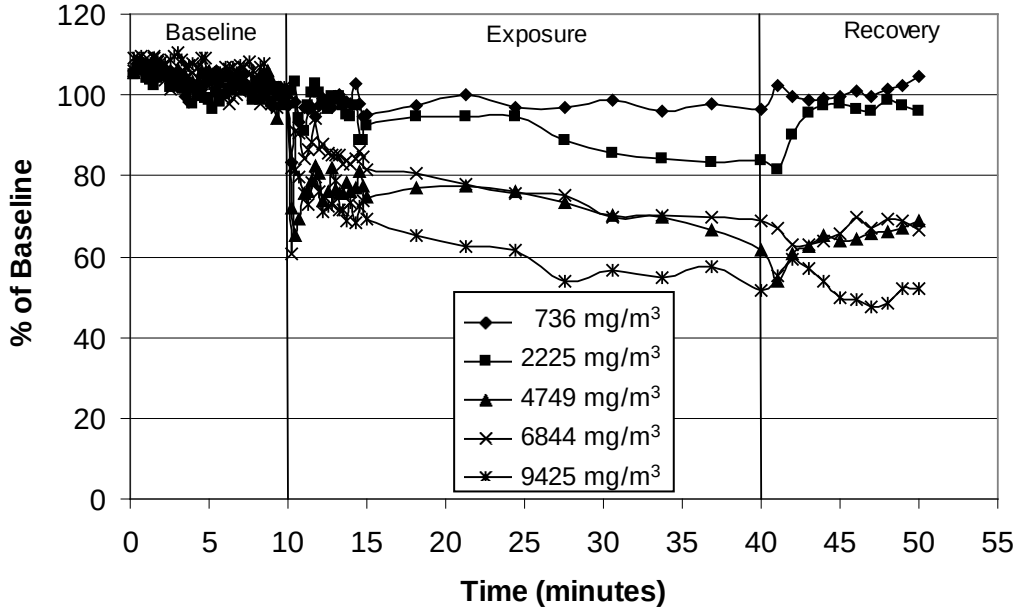

Figure 9. Group Mean Respiratory Rates (Percent of Baseline)

Group mean respiratory rates were decreased from baseline values 53, 33, 41, 21 and 10 percent at mean exposure concentrations of 9425, 6844, 4749, 2225, and 736 mg/m^3, respectively. The response of each animal was graded on a scale of slight, moderate or extreme, shown in Table 10. A decrease in respiratory rate of 12 to 20 percent was graded as a slight response, 20 to 50 percent as a moderate response, and 50 to 85 percent as an extreme response. Two mice in the lowest exposure group (736 mg/m^3) showed no response similar to what was seen in the jet fuel, JP-4, which also had two animals with no response at the vapor only exposure (Whitman and Hinz, 2001). One mouse (#15) in the mid exposure group (6844 mg/m^3) showed no response while the other three mice had moderate to extreme response. The difference in response could not be explained by visual observations of the animals, so there was no reason to exclude mouse #15 from the calculations.

The mice exposed to the higher concentrations of FT jet fuel (9425 and 6844 mg/m^3) showed decreased recovery (64 and 74 percent of baseline, respectively) compared with the lower concentrations which showed complete recovery (102 percent at 2225 mg/m^3 and 110 percent at 736 mg/m^3). Other studied also reported depressed recovery in sensory irritation studies with JP-4, JP-8, JP-8+100 fuels (Whitman and Hinz, 2001 and JP-5 (Whitman and Hinz, 2004), especially at the higher exposure concentrations.

4.2.3 RD_{50} Calculations. Figure 10 presents a graph of exposure concentration vs. respiratory rate decreases. The curve fell short of the 50 percent and was extended. The exposure concentration of FT jet fuel that would produce a 50 percent decrease in respiratory rate was calculated to be 11661 mg/m^3, with 95 percent confidence limits of 6885 to 38103 mg/m^3.

Alternative RD_{50} calculations were performed which omitted the data point at 4749 mg/m^3 because only the nominal and not the measured concentration was available. The vapor-only data point at 735 mg/m^3 was also omitted, as a similar point was not included in RD_{50} calculations for JP-8 jet fuel (Whitman and Hinz, 2001). The revised RD_{50} was calculated to be 10939 mg/m^3 (Figure 11).

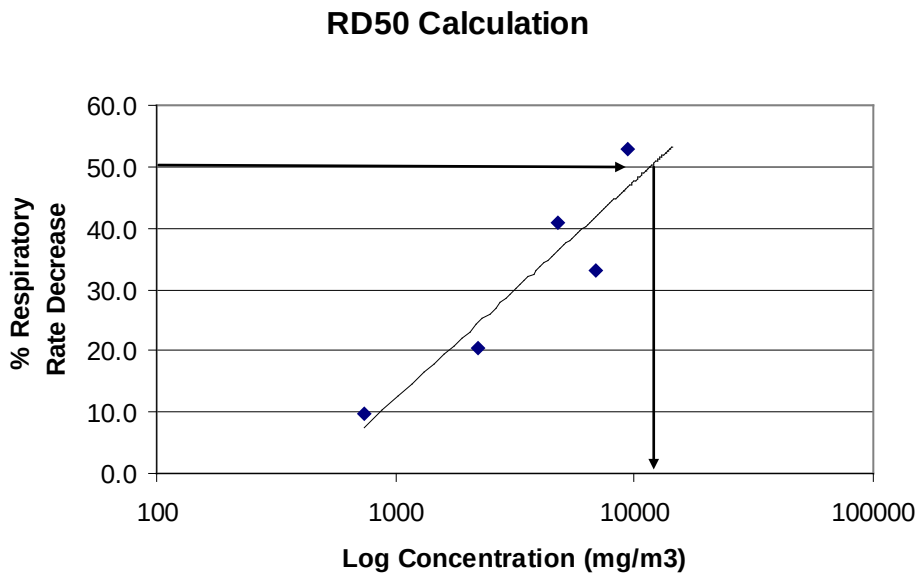

Figure 10. RD_{50} Calculation for FT Jet Fuel
Vapor-only and all vapor/aerosol data were included in the calculation. The RD_{50} was calculated as 11661 mg/m^3.

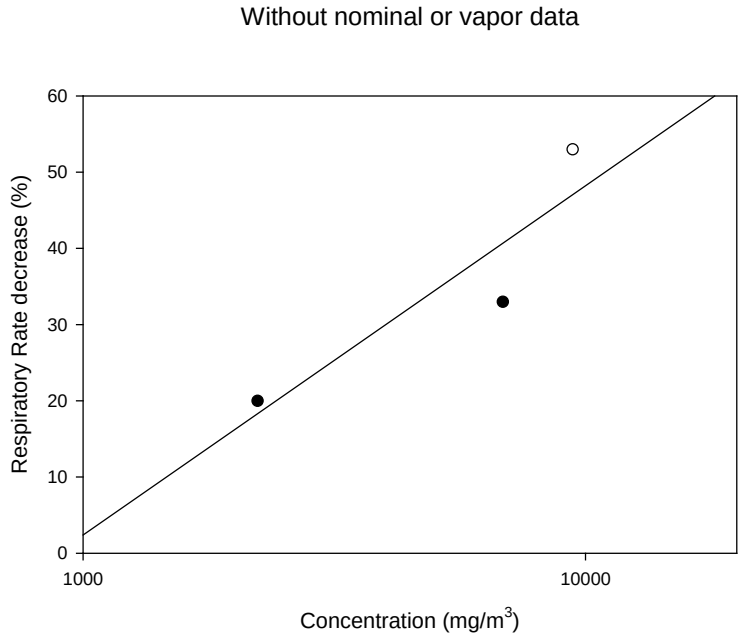

Figure 11. RD_{50} Recalculation for FT Jet Fuel
Vapor-only data and vapor/aerosol with nominal concentration (4749.3 mg/m^3) are excluded. The RD_{50} was calculated as 10939 mg/m^3.

4.3 Sensory Irritation Study Discussion

Exposures to atmospheres of FT jet fuel produced breathing patterns characteristic of upper airway sensory irritation in mice. Within the context and limits of this study, examination of the breathing patterns revealed no apparent pulmonary irritation. The vapor only exposure, in addition to defining the practical maximum vapor concentration without significant aerosol that still reflected all of the fuel's constituents, was an attempt to compare the animals' responses to vapor with a comparable vapor and aerosol concentration. Due to the saturation of FT vapor at this concentration and the need to expose mice at much higher vapor and aerosol concentrations, this comparison was not possible. The vapor-only concentration was not used for determining the RD_{50} value. One concentration was not able to be directly measured, so it was also not used to determine the RD_{50} value. The ASTM guideline does not specify a minimum number of concentrations but at least 3 concentrations are necessary to produce a regression line, the RD_{50} and its 95 percent confidence limits using the method of least squares. Based on three suitable concentrations, the RD_{50} for FT was determined to be 10939 mg/m^3. This value was then used in the HHA and OEL determination in the next section. The RD_{50} for FT will be compared to JP-8 as part of the HHA.

5.0 HHA AND OEL RECOMMENDATION

5.1 Data Sets – Traditional Jet Fuels vs. FT Jet Fuel

Table 11 compares the FT data set to available data from traditional jet fuels. According to the COT, data gaps still exist for chronic and carcinogenic studies of JP-8 (NRC, 2003). These two areas are also data gaps for FT fuel. Based on what is known about kerosene-based jet fuels, including the results of the FT jet fuel studies, these data gaps may not be critical. Developmental and reproductive endpoints are potential data gaps for FT jet fuel but again, based on what is known and the results of the FT jet fuel 90-day study in male and female rats, reproductive endpoints may not represent critical data gaps. However, these endpoints will be considered potential data gaps in this comparison (Table 11).

Table 11. Existence of Toxicological Data for Petroleum Derived and FT Jet Fuels

	JP-5 & 8 Jet A & A-1	FT	FT Data Gaps
Acute	✓	✓	
URT Irritation	✓	✓	
Two-week	✓*	✓	
Subchronic	✓	✓	
Chronic	-	-	?
Cancer	-	-	?
Immunological	✓	-	?
Neurological	✓	✓	
Developmental	✓	-	?
Reproductive	✓	-	?
Genotoxic	✓	✓	

Notes: "-" = no data; ✓ = data available; * = technical report by Naval Medical Research Unit (NAMRU)/Dayton is in preparation; ? = potential data gap

5.2 OELs and Sensory Irritation

Alarie (1981) reported a correlation between the TLVs set by ACGIH and 3 percent of the RD_{50} for a given chemical. It was found that TLVs already determined by ACGIH fell between 1 and 10 percent of the RD_{50} value for all chemicals for which a TLV and RD_{50} were available. Three percent represents the log of the mid-point in the range between 1 and 10 percent; thus, the 3 percent value of an RD_{50} represents a potential target value for OEL development for a given chemical. It is necessary to apply all available toxicological data for a chemical before defining the OEL.

Exposure limits have been determined for JP-8 by various regulatory agencies (Table 12). A comparison was made for RD_{50} values between JP-8 (Whitman and Hinz, 2001) and FT jet fuel in Table 13. A comparison of effect levels and uncertainty was made for FT jet fuel based on the two-week and 90-day inhalation studies (Table 14).

Table 12. JP-8 Exposure Limits

Agency	Limit Type	Explanation	Limit [mg/m^3]
NAC	AEGL-I	3 degrees of severity across 5 time periods	290
	AEGL-II		109
	AEGL-III		ND (no mortality)
ACGIH	TLV	Kerosene & jet fuel	200 (vapor)
	STEL, IDLH		NA
	Warning	Skin & respiratory irritation; Aerosols more irritating	
COT	Guidance		5 (aerosol); 200 (vapor)
AFOSH 48-8 (1997, rescinded 2008)	OEL TWA	1997 Standard: *Controlling Exposures to Hazardous Materials*	200
	STEL		1800

Notes: NAC = National Advisory Committee; AEGL = Acute Exposure Guideline Levels; ND = not determined; ACGIH = American Conference of Governmental Industrial Hygienists; STEL = Short Term Exposure Level; IDLH = Immediately Dangerous to Life and Health; NA = not applicable; COT = National Academies of Science, Committee on Toxicology; AFOSH 48-8 = Air Force Occupational Safety and Health Standard 48-8; OEL-TWA = Occupational Exposure Limit, Time Weighted Average

Table 13. Comparison of RD_{50} Levels between JP-8 and FT Jet Fuel

	JP-8	FT
RD_{50} (mg/m^3)	2876	10939
1%	29	109
3%	86	328
10% (threshold)	288	1094
maximum vapor	708	736

Table 14. Comparison of Effect Levels and Uncertainty for FT Jet Fuel with Exposure Guidance for JP-8

Fuel		mg/m^3
FT	NOAEL (2 week – subchronic)	200 - 500
	LOAEL (2 week – subchronic)	700 - 1000
JP-8	COT Guidance	5 / 200 aerosol / vapor

Notes: NOAEL = no observable adverse effect level; LOAEL = lowest observable adverse effect level

6.0 TOXICOLOGY PROGRAM SUMMARY

The FT jet fuel toxicology program assembled a multi-disciplinary team that defined key data requirements and designed the appropriate toxicology studies. All studies were conducted under GLP and regulatory test guidelines. The FT jet fuel database that was developed is now comparable to the database for JP-8. A summary of the toxicity findings for FT jet fuel is found in Table 15.

Table 15. FT Jet Fuel Toxicity Summary

Study	Finding
Dermal Irritation	Slightly to moderately irritating
Genotoxicity	Not genotoxic (3 assays)
	Not mutagenic or clastogenic
	Not likely to be frankly carcinogenic
Inhalation Toxicity	
Acute study	Unremarkable
2-Week study	Effects minimal – mild, NOAEL = 500-1000 mg/m^3
Subchronic study	Effects minimal – mild; NOAEL = 200-700 mg/m^3
	Significant changes limited to highest dose
	No effect level = 200 mg/m^3
Sensory Irritation	Upper airway sensory irritant
	RD_{50} = 10939 mg/m^3

7.0 RECOMMENDATION FOR INTERIM OEL

FT jet fuel is being certified for Air Force use as a 50/50 blend of FT jet fuel and JP-8. Therefore the OEL recommendation has to involve both 100 percent FT jet fuel and the 50:50 blend with JP-8. The OEL is based on the comparative toxicity of FT jet fuel versus JP-8. FT jet fuel is comparable to JP-8 and is actually less toxic or hazardous than JP-8 based on the toxicity data. For safety's sake, a conservative approach is always better. If the "more hazardous" fuel defines the OEL Environmental Safety and Occupational Health (ESOH) guidance, then JP-8's OEL and ESOH practices should be adopted as the recommended OEL for FT jet fuel. These guidelines are established and familiar to all personnel. If the OEL for FT jet fuel is 200 mg/m^3 and JP-8 is 200 mg/m^3, then the blended fuels would also be 200 mg/m^3.

8.0 FUTURE DIRECTIONS

Air Force guidelines are part of AFOSH 48-8, an umbrella for specific OELs. However, AFOSH 48-8 has been rescinded, leaving the risk assessment process to personnel on site using operational risk management principles to assess potential hazards. Guidance is still needed, especially with new classes of alternative jet fuels. The USAFSAM Mission will be to provide guidance governing the use of jet fuels and potential exposures. An HHA and OEL guidance document is being drafted by USAFSAM for kerosene-based fuels, FT derived fuels, and other synthetic fuels which can also serve as a predicate for ESOH policy.

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LIST OF ABBREVIATIONS

AAALAC	Association for the Assessment and Accreditation of Laboratory Animal Care
ACGIH	American Conference of Industrial Hygienists
AFB	Air Force Base
AFCO	Alternative Fuels Certification Office
AFIOH	Air Force Institute for Operational Health
AFRL	Air Force Research Laboratory
API	American Petroleum Institute
APS	aerodynamic particle sizer
ASTM	American Society for Testing and Materials
ATSDR	Agency for Toxic Substances and Disease Registry
COT	National Academies of Science, Committee on Toxicology
CRADA	Cooperative Research and Development Agreement
DFM	diesel fuel marine
DoD	Department of Defense
ESOH	Environmental Safety and Occupational Health
FMI	fluid metering intake
FT	Fischer-Tropsch
GLP	Good Laboratory Practices
HEPA	high efficiency particulate air
HHA	health hazard assessment
HPV	high production volume
IACUC	Institutional Animal Care and Use Committee
IR	Infrared
LOAEL	lowest observable adverse effect level
MRL	minimum reference level
NAC/AEGL	National Advisory Committee for the Development of Acute Exposure Guideline Levels for Hazardous Substances
NAMRU	Naval Medical Research Unit
NOAEL	no observable adverse effect level
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PEL	permissible exposure limit
RD_{50}	50 percent respiratory rate depression
S-8	synonym for FT jet fuel
SD	standard deviation
SPK	synthetic paraffinic kerosene
STEL	short term exposure limit
THRU	Toxic Hazards Research Unit
TLV	threshold limit value
U.S. EPA	United States Environmental Protection Agency
URT	upper respiratory and trachea